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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Prophylactic and Therapeutical Preparation Against Caries

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(30) (DE) P 42 21 054.2 1992/06/30

(57) 12 Claims

5,101,0/79

Preparation for the Prophylatic and Therapeutic Treatment of Caries

The invention concerns a preparation for the prophylatic and therapeutic treatment of caries, in the form of a chewable mass, chewable sweets, sucking sweets, toothpaste, mouth wash, mouth spray and similar.

With caries, point-by-point destruction of the tooth enamel and, from time to time, also of the dentine underneath, causes lesions. As a preparative measure to save the tooth, the damaged region of the dental enamel and the dentine is first removed with the aid of a drill so that a cavity is formed. After disinfecting, the cavity is filled through the insertion of certain materials in the form of amalgam, plastic, cement, gold or similar in order to prevent dirt, bacteria from entering. Finally, the surface of the filling material and especially the surface of the transition zone is polished to prevent the reoccurrence of caries.

It is to be seen as disadvantageous that the prior art method is costly and under circumstances requires more than one visit to the physician.

It is the object of this invention to provide a preparation for remineralisation, the use of which creates optimum conditions

in the oral cavity and/or directly at the tooth.

This object is solved therein that it is proposed to provide a proton donor as well as dissolved or easily soluble calcium and dissolved or easily soluble phosphate. The preparation is used orally, e.g. in the form of a sucking or chewable sweet or a chewable mass. Toothpaste, mouth wash, mouth spray or other preparations for daily dental and oral hygiene can also be viewed as vehicles.

The invention is based on the recognition that the process causing caries is reversible. Results from both experimental tests as well as a mathematical diffusion-reaction model show that the non-stationary marginal conditions for the mineral exchange processes at the teeth are especially important: only adequately varying concentrations of dissolved mineral (essentially calcium and phosphate) and the pH value and inactive ingredients such as fluoride in the oral cavity environment, which rinse the lesion, facilitate a complete and deep remineralisation of the lesion. The same processes play an important role in the prophylactic saturation of the hard dental substance with minerals.

The mineralisation process described is largely defined by physico-chemical values such as the deposition rate of mineral from the dissolved phase, the saturation concentration at the respective pH value, or the

diffusion constants of the different dissolved components. These parameters and the substrate surface, i.e. the active surface in the enamel, influence the quantity, type and structure of the deposited mineral.

These processes viewed initially in vitro also function in viva.

The exploitation of this recognition in order to develop a caries prophylactic or therapy is largely defined by the possibility of creating the optimum conditions in the oral cavity or directly at the tooth. This also includes the creation of optimum conditions for remineralisation, which lie in the acidic range. The addition of a proton donor serves to generate (initially from a neutral condition) a low pH value. Only then are the calcium and phosphate bonds dissociated.

For a sucking sweet, sugar or sugar substitutes such as xylite, sorbit or isomalt can be used the as base mass. Further possibilities consist of sugar substitutes and/or gelatine and/or gum arabic and/or chewable mass.

In the formulation of a recipe for an application, the buffer action of the residual phosphate and that of the saliva must be considered. An important point of view for the composition is also the saliva clearance, i.e. the quantity of introduced agents which are diluted and swallowed via the saliva. This proportion is greatly influenced by the form of

application (sucking sweet, chewable sweet, toothpaste ...). In the case of an initial pH value of pH=4-4.5, which is required for a controlled remineralisation, one part of the phosphate is provided as H2PO4 ion, i.e. only simply dissociated in solution. The undissociated protons, fixed to the phosphate, must be additionally added. This can be done, e.g., in the form of citrate or another acid used in confectionery making for aromatising (e.g. lactic acid, malic acid, tartaric acid, general fruit acid). The use of calcium chloride as a calcium donor is also conceivable.

To delay the clearance of the substances deriving from the device and therefore to control the concentration profiles, substances can also be added to the devices, especially the toothpaste, the mouth wash and the mouth spray, which, on the one hand, physically bind calcium and/or phosphate in large quantities, on the other hand, are themselves adsorbed on the tooth surface and/or oral cavity mucous membrane. Such substances are mostly of organic nature and bipolar and are used as fluoride carriers in caries therapy, such as amine fluoride. Substances from the class of the chlorhexidine digluconate and the quarternary ammonium bases are also used for similar purposes, e.g. to prolong the disinfecting effect (e.g. with chlorhexidine and benzoxonium chloride).

But also additions of higher viscosity which are deposited on the tooth and the mucous membrane and which can contain adsorbed calcium and phosphate adsorbed, can be considered to delay the clearance. Nature forms such substances, e.g., in the dental plaque in the form of extracellular polysaccharides. Therefore, such an addition can, e.g., be a substance from the class of the polyglucans.

In an acidic environment, Ca-PO4 often does not precipitate in a solid form or in the most favourable energetic form, hydroxylapatite. Therefore, escort substances are to be added to the formulation, which act as catalysts for the formation of solid hydroxylapatite and to avoid fractional deposition. For example, fluoride is known as such a substance.

The explanations show that there are different formulations for the composition of the preparation depending on the kind of application:

a) For sucking sweets or chewable sweets with an average retention time of 5-8 minutes in the mouth, the mechanism described above, while considering salivation, can be realised through the following composition. The constant loss of mineral components through swallowing of the solutions is taken into account:
Per kg of sweet mass, 200 to 800 mM, preferably 300 to 600 mM, especially 400 to 500 mM of calcium or calcium compounds must be

added, which corresponds to more or less 0.9 to 3.6 weight per cent, 1.35 to 2.7 weight per cent and 1.8 to 2.25 weight per cent respectively of calcium (compounds).

Because of the existing high phosphate content (content of phosphate ions) of the saliva, the supply of phosphate (ions) through the described device can be limited to between 50 and 400 mM, especially 100 to 300 mM. Expressed in weight per cent: 0.47 to 3.73 or 0.94 to 2.82 per cent PO4.

One part of the protons required for acidifying is buffered by phosphate (ions). For this reason and through the incomplete dissociation of the different fruit acids, it is lost for the acidification of the oral cavity environment. The addition of acid is governed by these conditions.

Required to acidify the oral cavity are 290 mM H^+ per kg of sweet mass (this value is based on measurements taken in the mouth).

Taking into account the aforementioned conditions, if a calcium fruit acid salt is used as a calcium donor, a fruit acid content of 400 to 1500 millival is required. Converted to the tribasic critic acids, this means, depending on the degree of dissociation, a content of approx. 2.8 to 11 weight per cent of citrate. To catalyse the solid disposition of hydroxylapatite, the sweet should also contain 0.7 to 2.4 mM of fluoride/kg of sweet.

b) For an application as toothpaste, considering the dilution effect through the saliva and its buffer capacity, a formulation in the following limits must be considered:

160 to 660 mM Ca, preferably 240 to 500 mM, especially 320 to 440 mM Ca and 40 to 330 mM, preferably 80 to 250 mM PO4. Of acid, one requires between 300 and 1200 millival. All data applies to 1 kg of toothpaste.

One part of the calcium and phosphate can, as described, be given in an adsorptive carrier.

The application form as toothpaste has the great advantage that, as also described below, it is distributed evenly in the mouth and creates very homogenous conditions. The carrier is especially important because of the relatively short retention time of the actual toothpaste in the mouth.

c) The concentrations in the mouth wash are lower than in the case of the other two formulations because of the relative large quantities of liquid that are taken up during rinsing. To create the most favourable conditions possible in the oral cavity for hardening the tooth enamel, a mouth rinse solution can be composed as follows:

5 to 22 mM Ca, preferably 8 to 16 mM, especially 10 to 15 mM Ca and 1 to 10, preferably 3 to 8 mM PO4 and 10 to 14 millival of acid/kg of mouth wash. These values refer to a ready-for-use solution with 30 ml/application. The formulations in examples b and c are also to be augmented with low doses of fluoride. During a certain time all of these formulations create an environment in the oral cavity in which the tooth enamel is impregnated with dissolved minerals from a saturated solution at a lowered pH value. Through the use of the acidic sweet or the washing out of the calcium and phosphate adsorptive carrier in toothpastes or mouth washes, there is an increase in the pH value on the surface and a concentration gradient between the surface of the enamel and its interior. This causes a diffusion current of protons, calcium and phosphate ions in the direction of the exterior environment. Because of the greater mobility of the protons compared with the calcium and phosphate ions, there is a faster increase in the pH value inside the enamel. This forces the calcium and phosphate ions under the enamel surface to precipitate and they are deposited as a solid material.

Figure 1 shows a measurement of the mass (= mineral) growth in a porous hydroxlapatite sample. Such samples behave like tooth enamel as concerns demineralisation and remineralisation, and as is known tooth

enamel consists primarily of this material. The samples were worn in the mouth on a dental plate and inserted three times daily during oral hygiene (5 minutes) in a solution with pH=4.5 which was saturated with calcium and phosphate.

As a control, in a second stage, the same sample was placed in distilled water and in a third experimental round again in the acidic calcium phosphate solution. The points on the diagram show the weight of the sample at the beginning of the test, after the first day with the acidic calcium phosphate solution, after one day with distilled water and then after a further day with an acidic calcium phosphate solution.

Obvious is a mineral increase of 1.4 mg after the two experimental stages with remineralisation solution, while the experimental stage with distilled water resulted in a mineral loss of 1 mg.

In the case of sucking a sweet with, e.g., 0.44 mole/kg Ca and 0.27 mole/kg PO4, with a acid content of 3.5% citric acid in the buccal cavity, the result is the temporal pH profile represented in Figure 2. After introduction of the sweet into the oral cavity, the pH value in the saliva falls within 1 minute to pH 4. Due to the cuboid design of the sweet, the disintegration of its surface is temporally essentially constant, so that per time the same quantity of acid always detaches. Therefore, a plateau

forms at about pH 4. After dissolution or removal of the sweet, the pH value in the saliva of the molar area again increases due to saliva clearance within 3.2 minutes. Corresponding curves with a higher pH plateau can be achieved with other acid contents.

ABSTRACT

Preparation for the Prophylactic and

Therapeutic Treatment of Carics

Proposed is a preparation for the prophylactic and therapeutic treatment of carics, in the form of a chewable mass, chewable sweets, sucking sweets, toothpaste, mouth wash, mouth spray and similar, whereby a proton donor and dissolved or easily soluble calcium and dissolved or easily soluble phosphate are provided.

- Figure 1 -

PATENT CLAIMS

1. Preparation for the prophylactic and therapeutic treatment of caries, in the form of a chewable mass, chewable sweets, sucking sweets, toothpaste, mouth wash, mouth spray and similar, **wherein** a proton donor and dissolved or easily soluble calcium and dissolved or easily soluble phosphate are provided.

2. Preparation according to claim 1, **wherein** as a base mass sugar or sugar substitute and/or gelatine and/or gum arabic and/or chewing mass is contained.

3. Preparation according to claim 1 or 2, **wherein** the proton donor is an organic acid, especially an acid used to aromatise confectionery, such as citric acid, lactic acid, fruit acid, tartaric acid or their mixtures.

4. Preparation according to one of claims 1 to 3, **wherein** the calcium compound is a calcium fruit acid salt.

5. Preparation according to one of claims 1 to 4, **wherein** in a solid state

the proportion of calcium is 0.9 to 3.6 weight per cent, preferably 1.35 to 2.7 weight per cent, especially 1.8 to 2.25 weight per cent and that of the phosphate is 0.47 to 3.73, especially 0.94 to 2.82 and a quantity of 400 to 1500 millival fruit acid per kilogram of solid mass.

6. Preparation according to one of claims 1 to 5, **wherein** with a toothpaste there is a proportion of 160 to 660 mM calcium compounds per kilogram preferably 240 to 500, especially 320 to 400 mM/kg and in the case of phosphate a proportion of 40 to 330 mM/kg preferably 80 to 250 mM/kg and the acid proportion is 300 to 1200 millival/kg of toothpaste.

7. Preparation according to one of claims 1 to 6, **wherein** with mouth wash the proportion of the calcium is 5 to 22 mM especially 10 to 15 mM and the proportion of the phosphate is 1 to 10, preferably 3 to 8 mM and the proportion of acid is 10 to 40 millival/kg.

8. Preparation according to one of claims 1 to 7, **wherein** the content of a substance that inhibits fractional precipitation, especially fluoride is in a concentration of 0.7 to 2.4 mM/kg.

9. Preparation according to one of claims 1 to 8, **wherein** a calcium and/or phosphate adsorptive substance is added.

10. Preparation according to claim 9, **wherein** the adsorptive substance is a polyglucan.

11. Preparation according to claim 9, **wherein** the adsorptive substance is a mucin.

12. Preparation according to claim 9, **wherein** the adsorptive substance is bipolar.

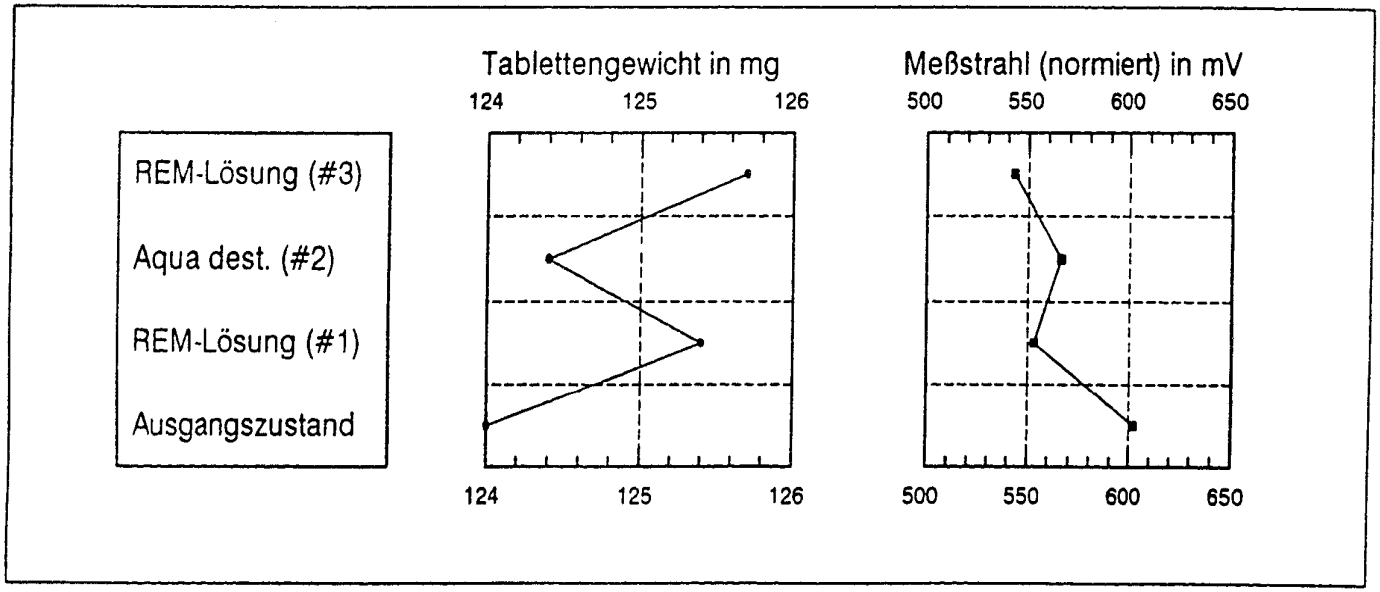
ERSATZBLATT

Abb.1

Intraorale DEM-REM

(Tablette #5, 24 Stunden intraoral pro Zyklus)

	Ausgangszustand	REM-Lösung (#1)	Aqua dest. (#2)	REM-Lösung (#3)
Tablette mit Ring (g)	0.3132	0.3146	0.3136	0.3149
Tablette (mg)	124.00	125.40	124.40	125.70
Referenzstrahl (V)	15.0700	15.2300	15.4300	15.6500
Meßstrahl (V)	0.6020	0.5590	0.5800	0.5640
Meßstrahl normiert (mV)	602.00	553.10	566.00	543.10



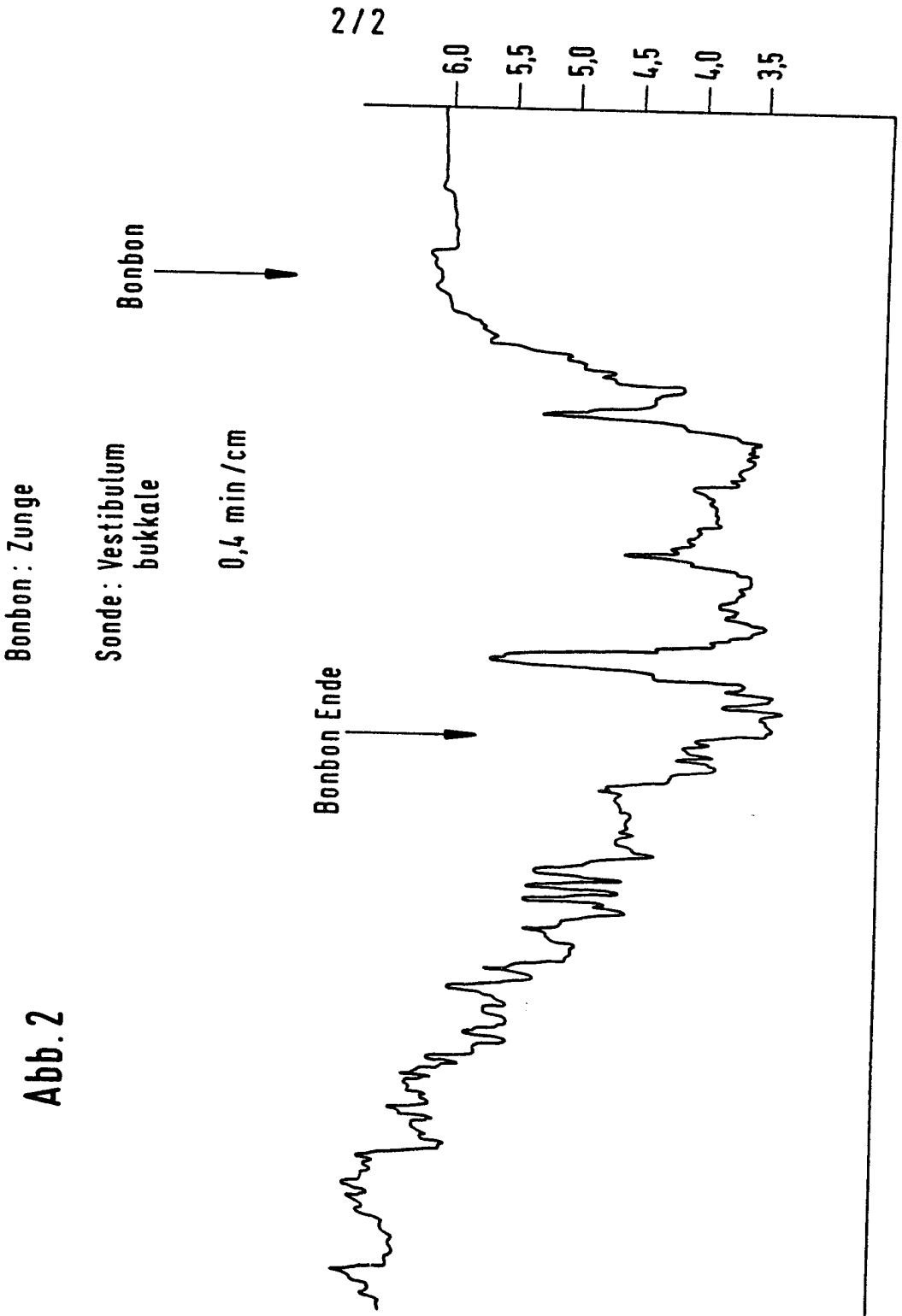

6,0
5,5
5,0
4,5
4,0
3,5
Bonbon
Bonbon Ende
Bonbon: Zunge
Sonde: Vestibulum bukkale
0,4 min/cm

Abb. 2